IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BUSH *et al.*

Appl. No. 09/380,704

§ 371 Date: June 6, 2000

For: **A Composition Comprising a Metal Chelator and a Method of Treating Amyloidosis by Administering the Metal Chelator**

Confirmation No.: 2953

Art Unit: 1647

Examiner: Bunner, B.

Atty. Docket: 0609.4350001/TJS/FRC

Reply Brief Under 37 C.F.R. § 1.193(b)(1)

Mail Stop Appeal Brief - Patents

Commissioner for Patents
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Sir:

Appellants filed a Brief on Appeal to the Board of Patent Appeals and Interferences for the above-captioned application on December 17, 2003. The appeal is directed to the final rejection of claims 1, 2 and 37 under 35 U.S.C. § 112, first paragraph, as set forth in the Office Action dated May 22, 2003. The Examiner's Answer was mailed March 23, 2004. In reply to the Examiner's Answer, Appellants submit this Reply Brief Under 37 C.F.R. § 1.193(b)(1).

I. Ritchie et al. (Exhibit 6) Was Timely Filed and Should be Fully Considered

The Examiner stated that the Ritchie *et al.* manuscript, which was submitted with the Appeal Brief as Exhibit 6, "was not timely filed and therefore [is] not considered by the Examiner." *See* Examiner's Answer at page 29. The Examiner also stated that, since the Ritchie manuscript "has not been peer-reviewed and its contents have not been

attested to under 37 C.F.R. 1.132 . . . arguments pertaining to the Ritchie unpublished manuscript are not found persuasive." *See* Examiner's Answer at page 29.

Appellants first note that the Ritchie *et al.* manuscript was originally submitted as Exhibit 2 with Appellants' Amendment and Reply Under 37 C.F.R. § 1.111, filed on February 26, 2003. Since the Ritchie manuscript was submitted before the mailing of a final Office Action, it was timely submitted and should be fully considered. Appellants also note that the Examiner fully considered the Ritchie manuscript in the Office Action that was mailed on May 22, 2003 (pages 9-10) and, at that time, made no indication that the manuscript did not "rise to the level of evidence." Finally, Appellants note that the Ritchie manuscript has been peer-reviewed and was published as Ritchie *et al.*, *Archives of Neurology 60*:1685-1691 (Dec. 2003).

II. The Examiner Has Taken Inconsistent Positions Regarding The Predictive Value of The Results Obtained with Other Chelators

Appellants maintain their position that the Examiner has not presented sufficient evidence or scientific reasoning to indicate that practicing the methods encompassed by the claims on appeal would have required undue experimentation on the part of a person of ordinary skill in the art. In addition, Appellants respectfully point out that the Examiner has taken two distinct, contradictory positions regarding whether the results obtained with one chelator are predictive of the results that would likely be obtained with another chelator.

To support the enablement rejection, the Examiner has cited references relating to the chelators TPEN and DFO. *See* Examiner's Answer at pages 7-8. Based on the reported "technical issues" relating to the use of these chelators, the Examiner has implied that similar issues would have been encountered with the administration of bathocuproine. On the other hand, in response to Appellants' assertion that the positive clinical results obtained with the chelator clioquinol are indicative of the results that would be obtained with bathocuproine, the Examiner has asserted that results with one chelator cannot be used to predict the results that would be obtained with another chelator. *See* Examiner's Answer at pages 29-31.

Presuming that the correct approach is that the results obtained with TPEN and DFO are indicative of the results that might be obtained with bathocuproine, then there is no logical or scientific reason to believe that the results obtained with clioquinol would not also be predictive of the results that would be obtained with bathocuproine. Thus, if the results observed with one chelator are indicative of the results obtained with another chelator, then the evidence of record cannot support a *prima facie* case of non-enablement, but instead supports the position that bathocuproine would be effective at treating amyloidosis when administered to a subject.

A *prima facie* case of non-enablement cannot be established unless the Examiner presents sound, scientifically-based evidence indicating that the practice of the claimed invention would have required undue experimentation. *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Appellants have submitted evidence in the example of Cherny *et al.* (2002) which relates to the testing of the chelator clioquinol in

the same "human brain amyloid extraction assay" provided by the present specification. In the case of clioquinol, it was on the basis of the results presented in this experimental assay that a person of skill in the art was able to both formulate this compound and carry out a successful clinical trial involving the administration of clioquinol without requiring undue further experimentation. Accordingly, in the absence of subjective evidence from the Examiner as to why a direct extrapolation from the situation presented in the clioquinol example to the situation presented in the present case cannot not be made, Appellants submit that a person of ordinary skill in the art is armed with a level of experimental support in the present case which is comparable to the support provided for clioquinol and so would be able to formulate and administer bathocuproine without undue experimentation. Consequently, Appellants submit that a *prima facie* case of non-enablement has not been established.

III. The Solubilization of Aβ From Brain Homogenates is Recognized in the Art as Being Predictive of the In Vivo Results of Metal Chelators

As noted in the Appeal Brief, the specification demonstrates that bathocuproine promotes the solubilization of Aβ from human brain homogenates. *See* Appeal Brief at page 8 (citing the Specification at page 91, line 18, through page 94, line 25). Thus, the specification provides substantial experimental evidence to indicate that bathocuproine would be effective at treating amyloidosis when administered to a subject. *See* Appeal Brief at page 8. The Examiner has dismissed the argument that the *in vitro* results presented in the specification are indicative of the results that would be obtained *in vivo* on the ground that "the utilization of brain homogenates in Examples 5-7 of the instant

specification (pg 90-121) is not an art-recognized, predictive model system for amyloidosis." *See* Examiner's Answer at pages 17 and 25. Appellants respectfully note that this is an incorrect statement.

The solubilization of Aβ from brain homogenates is recognized in the art as being predictive of the *in vivo* results of metal chelators. Clioquinol, which has been shown to be effective in the treatment of Alzheimer's disease, was originally found to promote the solubilization of Aβ from brain homogenates. *See* Cherny *et al.*, *Neuron 30*:665-676 (2002) (submitted as Exhibit 1 with Appellants' Amendment and Reply Under 37 C.F.R. § 1.111, filed February 26, 2003, and as Exhibit 7 with the Appeal Brief). The brain homogenate assay system that was used for clioquinol is the same as that which was used in the present specification for bathocuproine. As noted in Cherny *et al.*:

> In order to confirm that CQ [clioquinol], like other Cu^{2+}/Zn^{2+}-selective chelators, could chemically solubilize Aβ deposits in AD (Cherny et al., 1999), we homogenized postmortem human brain samples affected by AD in the presence of CQ. We found that there was a concentration-dependent increase in Aβ liberated into the soluble phase, typically >200% in the presence of ≥0.4 μM CQ (Figure 1C, typical of 9 cases). . . . *The effect of CQ in enhancing Aβ liberation in this assay is comparable to the effect we previously reported in the same system for bathocuproine, a Cu^{+} chelator* (Cherny et al., 1999). Similar to the effects of homogenizing the brain sample with other Cu/Zn-selective chelators (Cherny et al., 1999), the majority (90%) of the Aβ remains in the pellet phase after one extraction with CQ.

Cherny *et al.*, paragraph bridging pages 666 and 667 (emphasis added).

Thus, it is clear that the solubilization of Aβ from brain homogenates is well-recognized in the art as an effective model system for the treatment of amyloidosis. In

addition, since clioquinol was subsequently found to be effective in the treatment of Alzheimer's disease, it is reasonable to conclude that the results obtained using the brain homogenate assay system are predictive of the results that would be obtained when the metal chelator is administered to a human subject. Indeed, it was on the basis of similar results from the same assay that the skilled artisan was able to formulate and carry out a successful clinical trial for clioquinol. The Examiner has not provided an objective basis for why a person skilled in the art, in view of the present specification, could not have done the same. It was improper for the Examiner to discount the experimental evidence in the specification which supports the enablement of the claimed invention.

IV. Conclusion

In light of the arguments above, as well as those set forth in Appellants' Brief on Appeal filed December 17, 2003, Appellants respectfully submit that the final rejection of claims 1, 2 and 37 under 35 U.S.C. § 112, first paragraph, is improper and should be reversed.

Respectfully submitted,
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Date: MAY 24, 2004

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